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(54) 6-SUBSTITUTED ACYCLICPYRIMIDINE NUCLEOSIDE DERIVATIVES AND ANTIVIRAL AGENTS CONTAINING SAME AS ACTIVE INGREDIENTS.

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JP-A- 5 032 186
JP-A- 5 188 974
JP-A- 5 738 774
JP-A- 5 785 373
JP-A- 6 156 171
JP-A-49 366 85

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EP 0 371 139 B1

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TECHNICAL FIELD

The present invention relates to novel 6-substituted acyclopyrimidine derivatives, antiviral agents containing the derivatives as the active ingredients and a process for preparation of the derivatives.

BACKGROUND ART

Infectious diseases caused by human acquired immunodeficiency virus (HIV), which is a type of retrovirus, have recently become a serious social problem. A compound of 3'-deoxy-3'-azidothymidine is known as a nucleoside compound used in the clinical treatment of HIV-infection. However, this compound has side-effects since it also exhibits considerable toxicity in the host cell.

Although some 2',3'-dideoxyribonucleosides are known as nucleoside compounds exhibiting an anti-retroviral activity, it is still necessary to develop a substance possessing a higher activity and lower toxicity to the host cell (Hiroaki Mitsuya, Bodily Defense, Vol. 4, pp. 213 to 223 (1987)).

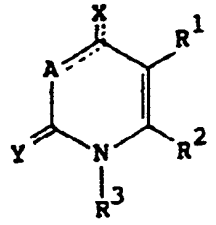
On the other hand, various acyclonucleoside compounds have been synthesized since Acyclovir (acycloguanosine) was developed as an antiviral substance effective against herpes virus (C.K. Chu and S.J. Culter, J. Heterocyclic Chem., 23, p. 289 (1986)). However, no acyclonucleoside compound having a sufficient activity especially against retroviruses has yet been discovered.

EP-A 46307 (or US-A 4415573), EP-A 49072, (or US-A 4347360), and EP-A 167385 disclose acyclopyrimidine nucleoside derivatives with some antiviral activity.

We have focussed our attention on 6-substituted acyclopyrimidine nucleoside compounds and have synthesized various novel 6-substituted acyclopyrimidine nucleoside derivatives and screened those compounds to detect an effective antiviral agent, especially to the retrovirus. Some 6-substituted acyclopyrimidine nucleoside compounds such as 6-fluoro substituted derivatives, 6-alkylamino substituted derivatives (DD-232492-A) and 6-methyl substituted derivatives (C.A. 107, 129717w (1987)), are known; however, the anti-retroviral activity of these compounds has not been described. As a result of our investigation, it was found that specific 6-substituted pyrimidine nucleoside compounds according to the invention satisfy the above demand which enables one to provide effective anti-retroviral agents.

SUMMARY OF THE INVENTION

The present invention concerns a 6-substituted acyclopyrimidine nucleoside derivative represented by the following general formula I:



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wherein R^1 represents a hydrogen or halogen atom or a group of alkyl, alkenyl, alkynyl, alkylcarbonyl, arylcarbonyl, arylcarbonylalkyl, arylthio or aralkyl; R^2 represents a group of arylthio, alkylthio, cycloalkylthio, aryl sulfoxide, alkyl sulfoxide, cycloalkyl sulfoxide, alkenyl, alkynyl, aralkyl, arylcarbonyl, arylcarbonylalkyl or aryloxy; R^3 represents a hydroxyalkyl group of which alkyl portion may contain an oxygen atom; X represents an oxygen or sulfur atom or amino group; Y represents an oxygen or sulfur atom; and A represents =N- or -NH-, or a pharmaceutically acceptable salt thereof. Compounds according to claim 1, wherein:

- R^1 represents a hydrogen atom; halogen atom; C_1 to C_{10} alkyl group; or a group of C_2 to C_5 alkenyl, C_2 to C_5 alkynyl, C_2 to C_5 alkylcarbonyl, C_7 to C_{11} arylcarbonyl, C_8 to C_{12} arylcarbonylalkyl, C_6 to C_{10} arylthio or C_7 to C_{12} aralkyl, those groups optionally substituted by one or more substituents selected from a halogen atom, C_1 to C_5 alkyl, C_1 to C_5 alkoxy, C_2 to C_6 alkoxycarbonyl, phenyl, naphthyl, carbamoyl, amino, nitro and cyano;

The group of R^1 represents a hydrogen atom; a halogen atom such as a chlorine, iodine, bromine and fluorine atom; an alkyl group such as a methyl, ethyl, n-propyl, i-propyl and n-butyl group; an alkenyl group such as vinyl, propenyl, butenyl, phenylvinyl, bromovinyl, cyanovinyl, alkoxycarbonylvinyl and carbamoylvinyl group; an alkynyl group such as an ethynyl, propynyl and phenylethynyl group; an alkylcarbonyl group such as an acetyl, propionyl and i-butyryl group; an arylcarbonyl group such as benzoyl and naphthoyl group; an arylcarbonylalkyl group such as a phenacyl group; an arylthio group such as a phenylthio, tolylthio and naphthylthio group; or an aralkyl group such as a benzyl group.

The group of R^2 represents an arylthio group such as a phenylthio and naphthylthio group, which may be optionally substituted with one or more substituents selected from a halogen atom such as a chlorine, iodine, bromine and fluorine atom, alkyl group such as a methyl, ethyl, propyl, butyl and pentyl group, halogenated alkyl group such as a trifluoromethyl group, alkoxy group such as a methoxy, ethoxy, propoxy and butoxy group, hydroxy group, nitro group, amino group, cyano group and acyl group such as an acetyl group; an alkylthio group such as a methylthio, ethylthio, propylthio, butylthio and pentylthio group; a cycloalkylthio group such as a cyclopentylthio, cyclohexylthio and cycloheptylthio group, which may be optionally substituted with one or more of the substituents mentioned above as the substituent of the arylthio group; an aryl sulfoxide group such as a phenyl sulfoxide group; an alkyl sulfoxide group such as a methyl sulfoxide, ethyl sulfoxide and butyl sulfoxide group; a cycloalkyl sulfoxide group such as cyclopentyl sulfoxide, cyclohexyl sulfoxide group; an alkenyl group such as vinyl, propenyl and phenylvinyl group; an alkynyl group such as an ethynyl, propynyl and phenylethynyl group; an aralkyl group such as a benzyl group; an arylcarbonyl group such as a benzoyl group; an arylcarbonylalkyl group such as a phenacyl group; or a aryloxy group such as a phenyloxy group.

The group of R^3 represents a hydroxyalkyl group, preferably an ω-hydroxyalkoxy alkyl group such as (2-hydroxyethoxy)methyl, (3-hydroxypropoxy)methyl, (2,3-dihydroxypropoxy)methyl, 1-(2-hydroxyethoxy)-ethyl, [2-hydroxy-1-(hydroxymethyl)ethoxy]methyl and (2-hydroxy-1-methylethoxy)methyl group.

The symbol of X represents an oxygen or sulfur atom or an amino group.

The symbol of Y represents an oxygen or sulfur atom.

The symbol of A represents =N- or -NH-.

The preferred compounds according to the invention have R^1 of a hydrogen atom, halogen atom, C_1 to C_5 alkyl group or C_2 to C_5 alkenyl group, particularly, C_1 to C_5 alkyl group; R^2 of C_6 to C_{10} arylthio, C_3 to C_{10} cycloalkylthio or C_7 to C_{11} aralkyl group, particularly those substituted with one or more substituents selected from halogen atom, C_1 to C_5 alkyl group, C_1 to C_5 alkoxy group and nitro group; R^3 of hydroxyalkoxyalkyl group having 2 to 6 carbon atoms, particularly 2-hydroxyethoxymethyl group; X of oxygen or sulfur atom; and Y of oxygen or sulfur atom.

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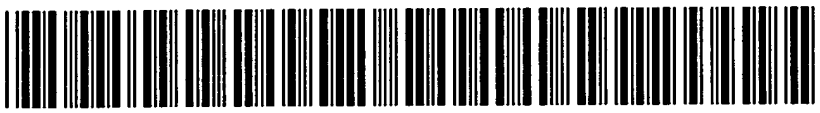

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